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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	15

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/058,546	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/30/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-53* is/are pending in the application.

4a) Of the above claim(s) *5-7, 12, 18, 24, 25, 29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8-11, 13-16, 19-23, 26-28 and 31-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14*
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-30-01, paper number 12, has been entered.

Applicant's arguments filed 1-30-01, paper number 13, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

1. Claims 33-53 have been added. Claims 1-16 and 18-53 are pending in the instant application. Claims 5-7, 12, 18, 24, 25, 29 and 30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 1-4, 8-11, 13-16, 19-23, 26-28, 31 and 32-53 are under consideration in the instant application as they relate to DNA. Claims with limitations directed toward antisense or DNA will be considered only as they relate to DNA.

Claim Rejections - 35 USC § 112

2. Claims 1, 3, 4, 15, 16, 19-23, 26-28, 31 and 32 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the office action of 5-24-99.

Claims 1, 33, 44 and 49 are directed toward a method of making a retroviral particle and recite using a producer cell, but the producer cells are not limited to isolated producer cells or performing the method *in vitro*. Claims 1, 33, 44 and 49 and claims dependent therefrom are rejected for reasons of record because applicants have not enabled performing the method *in vivo* or other *in vivo* embodiments. Claims 13, 39, 45 and 50 are directed toward producer cells but are not limited to isolated producer cells. Claims 13, 39, 45 and 50 and claims dependent therefrom are rejected for reasons of record because applicants do not enable making or using the producer cells *in vivo*. Limiting the claims to "isolated" producer cells in every instance of the term producer cell would overcome this rejection.

The specification does not provide adequate guidance correlating the results obtained *in vitro* to results obtained *in vivo* in such a way that one of skill would have a reasonable expectation in obtaining a therapeutic level of expression of SDI-1 such that cancer or restinosis could be treated. While an exact correlation is not required to enable an invention (page 7, line 20 of arguments), a reasonable correlation must be provided. The specification does not teach the level of SDI-1 required to obtain a therapeutic effect, the dosage, route of administration or the

desired therapeutic effect such that one of skill would be able to determine how to use the retroviral vector as a pharmaceutic composition (claims 19-20). In particular, it is unclear what therapeutic effect can be obtained by obtaining more cells in G_0/G_1 or how bladder carcinoma correlates to breast cancer (claim 23) or restinosis (claims 22 and 28). Therefore, the specification does not provide a reasonable correlation between obtaining bladder carcinoma in G_0/G_1 *in vitro* and *in vivo* uses of the retroviral particles.

Applicants argue the specification teaches that the dosage depends upon the mode of administration, form in which delivered, etc. The dosage, mode of administration and vehicle of delivery are parameters which are essential to the invention and would require undue experimentation to determine given the unpredictability in the art. The specification does not enable any pharmaceutic compositions, use of a retroviral vector for treatment of disease or methods of introducing retroviral particles for the purpose of therapy as claimed.

Applicants argue that one of skill in the art would be able to determine amino acids 1-71 or 42-58 of the human SDI-1 as claimed in claims 3 and 4 given the teachings provided in the specification because the specification states that SDI-1 is described in WO-A1-95/06415 (page 8, lines 20-21). Applicants have enabled one of skill to determine amino acids 1-71 or 42-58 of the human SDI-1 gene disclosed in WO 95/06415 but not any other human SDI-1, WAF1, CIP1, PIC1 or p21 sequence disclosed in the art (see page 2, line 2 of specification). It is not clear that any other amino acids of human SDI-1, WAF1, CIP1, PIC1 or p21 would have the same amino acid sequence or function as amino acids 1-71 or 42-58 described in WO 95/06415. The amino

acid sequence encoding human SDI-1, WAF1, CIP1, PIC1 or p21 varies in the art; therefore, one of skill would not be able to determine what applicants consider amino acids 1-71 or 42-58 of SDI-1 other than the sequence disclosed in WO 95/06415.

Applicants argue routine methods could be used to determine functionally equivalent analogues or fragments of SDI-1. Applicants argument is not persuasive. The specification has not taught any method to identify functionally useful analogues or fragments of the human SDI-1 gene taught in WO 95/06415. Such methods are not routine and are considered essential to determine functionally equivalent analogues or fragments as claimed.

Applicants argue the encapsulated cells and a pharmaceutical composition comprising packaging cells are enabled because the *in vitro* bladder carcinoma example in the specification enables *in vivo* therapeutic uses of such compositions. Applicants argument is not persuasive. The only disclosed use for encapsulated cells and pharmaceutical compositions in the specification is for administering the cells *in vivo* to obtain therapeutic effects (page 8, lines 5-19). The administration of replication competent retroviral packaging cells would most likely result in toxic, non-therapeutic results. Retroviral packaging cells are known to produce replication competent retroviral particles which, upon introduction to an individual, would prevent obtaining therapeutic effects. The specification does not provide adequate guidance such that one of skill could prevent production of replication competent retroviral particles or administer retroviral packaging cell lines such that a therapeutic effect could be obtained. The specification does not

teach the dosage, route of administration, level of retroviral particles secreted or level of SDI-1 expression required *in vivo* to use encapsulated retroviral packaging cells to treat any disease.

3. Claims 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite limitations wherein the recombinant retroviral particle is administered as an injection or by implantation of a packaging cell line. However, the claims refer to claim 28 which is limited to delivery of a packaging cell line. It is unclear whether applicants intend to claim administering retroviral particles or retroviral packaging cells.

Applicants argue that claims 31 and 32 are dependent upon claim 27 which is dependent upon claim 1. Claims 31 and 32 are dependent upon 28 which is dependent upon 27 which is dependent upon 13 which is independent.

Claim Rejections - 35 USC § 102

4. Claims 1-4 and 9 remain rejected and claims 13, 19, 26, 33, 34, 39, 43, 44, 45, 48, 49, 50 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsang (Tsang et al., 1994, Vaccine Res., Vol. 3, page 183-193) for reasons of record.

Tsang taught making retroviral particles comprising DNA encoding human p21 ras by transfecting a packaging cell line with a retroviral vector encoding human p21 ras operatively linked to the MT-1 promoter, wherein the packaging cell line contains a DNA construct required for retroviral packaging, and isolating retroviral particles encoding human p21 ras (page 185,

second paragraph). p21 is equivalent to SDI-1 (page 2, line 2 of the specification). The retroviral particles are used to infect B cells which is equivalent to infecting human cells with a retroviral particle as in claims 26, 43, 48 and 53. The pharmaceutical composition comprising the producer cell and a pharmaceutically acceptable carrier (claim 19) is anticipated by Tsang because Tsang teaches packaging cells in media which is a pharmaceutically acceptable because it is at physiological pH levels. The packaging cells of Tsang are equivalent to "producer cells" claimed (claims 13, 39, 45 and 50). The full length p21/SDI-1 protein of Tsang is greater than 58 amino acids; therefore, the retroviral vector encoding full length p21 encodes amino acids 1-71 of SDI-1 (claims 3, 44, 45 and 48) and amino acids 42-58 of SDI-1 (claims 4, 49, 50 and 53). The limitation of a target cell specific regulatory element or "target cell specific promoter" (claims 9 and 36) are equivalent to the MT-1 promoter because it is used to target specific cells.

Applicants argue Tsang does not teach the limitations of the claim. Applicants argument is not persuasive. The p21 protein of Tsang is the same protein as the SDI-1 protein disclosed in the instant invention and encodes SDI-1 protein, which inherently comprises amino acids 1-71 and 42-58 as claimed and inherently inhibits cell proliferation.

Claim Rejections - 35 USC § 103

5. Claims 1-4, 8, 13, 14, 19, 26-28, 31 and 32 remain rejected and claims 33, 35, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Miller et al., 1989,

Biotechniques, Vol. 7, pages 980-990) or Price (Price et al., 1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel (Nabel et al., US Patent 5,863,904, Jan 26, 1999).

Miller taught producing retroviral particles comprising transfecting packaging cells, PA317, with a retroviral vector encoding β-gal with a 5' LTR (see page 981, column 1, column 3). The PA317 packaging cell line taught by Miller is equivalent to a "producer cell" and is used in the instant invention (page 28, line 9). Price taught producing BAG retroviral particles using the packaging cell line NIH 3T3 (page 156, column 2, line 18). NIH 3T3 are "producer cells" because have a DNA construct coding for proteins for packaging and produce retroviral particles and is used in the instant invention (page 22, line 17). Miller and Price do not teach making retroviral particles encoding SDI-1 or producer cells transfected with a retroviral vector encoding SDI-1.

However, at the time of filing, Nabel taught making retroviral vectors comprising the gene encoding human p21 (see abstract; column 3, line 10; column 4, line 60). The gene encoding p21 taught by Nabel is SDI-1 as claimed because SDI-1 and p21 cause cells to accumulate in G_0/G_1, because the specification states SDI-1 is also known as p21 (page 2, line 2) and because Nabel states SDI-1 is equivalent to p21 (column 1, lines 22-23). Nabel administered the retroviral vectors encoding p21 to treat restinosis (see claims) or breast cancer (column 5, line 10) which is equivalent to administering a therapeutically effective amount of a retroviral particle encoding p21 as in claim 27. The full length p21/SDI-1 protein of Nabel is greater than 58 amino acids; therefore, the retroviral vector encoding full length p21 encodes amino acids 1-71 of SDI-1 (claim

3) and amino acids 42-58 of SDI-1 (claim 4). Nabel taught producing viral particles in human 293 packaging cells which makes the human producer cells (claim 14) (column 6, line 32). The intratumoral injection of Nabel is injection into the site of the tumor (claim 31, line 9). Injection of an encapsulated viral vector (claim 1 of Nabel) is equivalent to claim 32.

It would have been obvious to one of ordinary skill at the time the instant invention was made to produce a retroviral vector using the method taught by Miller or Price to make the retroviral vector encoding p21 as taught by Nabel. One of ordinary skill would have been motivated to produce retroviral vectors encoding p21 using the methods taught by Miller or Price to treat disease. Additional motivation is provided by Miller by stating the retrovirus can be used *in vivo* (page 989, last sentence) and by Price by teaching retroviral particles can be used to deliver genes of interest *in vivo* (page 157, column 1, fourth paragraph).

Applicants argue that Nabel only teaches transiently transfecting producer cells lines. However, Miller and Price teach stably transfecting producer lines. Furthermore, stably transfected does not differ from the transiently transfected producer cells of Nabel because they are stably transfected for a short amount of time. "Stably transfected" does not exclude temporarily, stably transfected cells as taught by Nabel.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is to treat restinosis as cited above.

6. Claims 1 and 9-11 remain rejected and claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (1989, Biotechniques, Vol. 7, pages 980-990) or Price (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel (US Patent 5,863,904, Jan 26, 1999) as applied to claims above, and further in view of Haertig (1993, J. Virology, Vol. 67, pages 813-821) for reasons of record.

The combined teachings of Miller or Price in view of Nabel teach methods of producing retroviral particles comprising transfecting packaging cells PA317 or NIH3T3 with a retroviral vector encoding p21 with a 5' LTR (see page 981, column 1, column 3 of Miller; page 156, column 2, line 18 of Price; see abstract; col. 3, line 10; col. 4, line 60; col. 1, lines 22-23). Miller or Price taken with Nabel do not teach using the MMTV regulatory elements.

However, at the time of filing, Haertig taught using MMTV regulatory elements in a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest (see page 819, column 2, first full paragraph; page 820, column 1, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of making a retroviral particle encoding p21 as taught by Miller or Price in view of Nabel with the MMTV regulatory elements taught by Haertig. One of ordinary skill would have been motivated to use the MMTV regulatory elements to target mammary tissue

as taught by Haertig to treat breast cancer as suggested by Nabel (col. 5, line 10). One of ordinary skill would have been motivated to target breast tissue to improve p21 expression in breast cancer and to obtain a greater therapeutic effect.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the references is to obtain mammary specific gene expression in treating breast cancer.

Claims 15, 16, 20-23, 41, 42 46, 47 51 and 52 appear to be free of the prior art of record because the prior art of record does not teach or suggest encapsulating packaging cells transfected with a retroviral vector encoding SDI-1 or treating a patient using such encapsulated packaging cells as claimed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C WILSON
PATENT EXAMINER